SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

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ANNEX E

Genetic hazards

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Introduction

1. The evaluation of genetic hazards associated with the exposure of human populations to ionizing radiation is one of the major areas in which the Committee has been active since its inception. Its first comprehensive Report on this topic was published in 1958 [U1], and this was followed by six Reports of a similar nature published in 1962 [U2], 1966 [U3], 1972 [U4], 1977 [U5], 1982 [U6] and 1986 [U7]. This time span of over a quarter of a century has witnessed a number of major advances in radiation genetics, human genetics, cytogenetics and epidemiology; it also represents a period during which, from the standpoint of genetic risk evaluation, there have been changes in concepts and methods and shifts in emphasis necessitating revision of views and quantitative estimates of genetic risks. The paucity of direct data that bear on the induction by radiation of genetic effects leading to disease states in man continues to remain a major drawback; however, the prodigious amount of literature on such effects in other species makes it prudent and reasonable to believe that exposure of human germ cells to ionizing radiation will cause mutations and chromosomal aberrations, which in turn may lead to diseases. So far, there has been no alternative but to use data generated from experimental organisms as the main basis for predicting expected effects in man; in fact, the estimation of genetic risks to man from exposure to ionizing radiation remains a major exercise in extrapolation.

2. The aim of this document is threefold: (a) to provide a general background of the principles and methods that are used in the evaluation of genetic radiation hazards in man; (b) to trace the evolution of the conceptual framework, the data-base, the assumptions and the extrapolations involved in genetic risk estimation, from about the mid-1950s to the present; and (c) to indicate in which areas research is in progress or needed in the years to come. While the emphasis will be on the Committee's continuing efforts in this direction, the work of other scientific bodies will also be discussed where appropriate.

A. GERM CELL STAGES AND RADIATION CONDITIONS RELEVANT TO GENETIC RISK EVALUATION

3. From the standpoint of hazard evaluations, it is the effects of radiation on two particular germ cell stages that are considered important: (a) the mitotically dividing stem-cell spermatogonia in the male, which constitute a permanent germ cell population in the testes and which continue to multiply throughout the reproductive life span of the individual, and (b) the oocytes, primarily the immature ones, in the female. Female mammals are born with a finite number of oocytes, formed during embryonic development. These primordial oocytes, as they are called, grow and become surrounded by follicles but are arrested at a particular stage (diplotene or dictyate) in meiosis. This arrest lasts from late pre-natal life until shortly before ovulation in the mature female. Because oocytes are not replenished by mitosis during adult life and because they only have to complete the meiotic divisions before pronuclear fusion, these are clearly the cell stages in the female whose irradiation has great potential significance for hazard evaluations.

4. The radiation exposures received by human populations are usually delivered as small doses at high-dose rates (e.g., exposure during diagnostic radiology) or they are greatly protracted (e.g., continuous exposure to natural and man-made sources). In therapeutic radiology, doses as high as several Gy may be delivered, and at high dose rates; however, such exposures are warranted on medical grounds and are given only to selected individuals for the treatment of specific cancers. In estimating genetic hazards to the population, the relevant radiation conditions are, therefore, low doses and low-dose rates.

B. GENERAL ASSUMPTIONS

5. In using the data from mouse studies (the principal model in this context) or studies of other suitable mammals (such as non-human primates) to make quantitative estimates of genetic risks in man, three important assumptions are made unless there is evidence to the contrary: (a) the amount of genetic damage induced by a given type of radiation under a given set of conditions is the same in human germ cells and in those of the test species used as the model; (b) the biological factors (e.g., sex, germ cell stage and age) and physical factors (e.g., quality of radiation and dose rate) affect the magnitude of the damage in similar ways and to similar extents in the experimental species from which extrapolations are made and in humans; and (c) at low doses and at low-dose rates of low-LET irradiation, there is a linear relationship between dose and the frequency of genetic effects. Other more specific assumptions and considerations will be discussed in the appropriate sections of this review.

C. METHODS

6. The methods that have been used so far in quantitative genetic risk assessments can be broadly grouped under two headings: the doubling dose method (or the relative mutation risk method) and the direct methods. The aim of the doubling dose method is to provide an estimate of risks in terms of the additional number of cases of genetic disease due to radiation exposure using the natural prevalence of such diseases in the population as a frame of reference.

7. The doubling dose is the amount of radiation necessary to produce as many mutations as those that occur spontaneously in a generation; it is obtained by dividing the spontaneous rate by the rate of induction per unit dose. Thus, for instance, if the average spontaneous rate is m_1 per locus and the average rate of induction is m_2 per locus per unit dose of radiation, then the doubling dose $c = m_1/m_2$. The reciprocal of the doubling dose, $1/c$, is the relative mutation risk per unit dose. It is easy to see that the lower the

doubling dose, the higher the relative mutation risk and vice versa.

8. The doubling dose method is generally used to estimate risks to a population under continuous irradiation. The general concept is that, under normal conditions in the absence of radiation, there is an equilibrium between those mutations that arise spontaneously and those that are eliminated by selection in every generation. Under conditions of continuous irradiation (with the influx of new mutations that it entails), the population will eventually reach a new equilibrium between those mutations that enter the gene pool and those that are eliminated.

9. In practice, what is done is to: (a) estimate the doubling dose(s) from experimental data on spontaneous and induced mutations and chromosomal aberrations and (b) estimate the expected increase at equilibrium as a product of prevalence, p, of spontaneously arising diseases, relative mutation risk, 1/c, and the dose sustained by the population. The increase in the first generation is then estimated from that at equilibrium, using certain assumptions. It bears mentioning that the risk at equilibrium under conditions of continuous irradiation (say, at a rate of x mGy per generation) is numerically equal to the integrated risk over all future generations following a single (i.e., one time only) dose of x mGy to the parental generation.

10. In principle, the doubling dose method can be used to estimate risks from the induction of mutational events, irrespective of whether they are operationally classified as dominants or recessives, as well as chromosomal aberrations. The major application of the above method, however, is to simple, dominantly inherited traits whose equilibrium frequencies (i.e., those of the responsible mutant genes) can be assumed to be directly proportional to the mutation rate [B1, D1]. The assumption is almost as good for sex-linked traits [B1].

11. An increase in mutation rate of autosomal recessive genes will not lead to a corresponding increase in the frequency of recessive diseases for two reasons: (a) when recessive mutations first arise (or are induced), they are present in heterozygous condition and their fate depends strongly on the way selection acts [B1] and (b) a recessive mutation has to combine with an already existing recessive allele or become homozygous to manifest the disease, and this may take from many to hundreds of generations, depending on a number of factors.

12. Evidence for the radiation induction of numerical chromosomal anomalies resulting in live births, either in experimental mammals or in man, is insufficient and equivocal, apart from XO induction in mice. Consequently, the use of the doubling dose method to estimate risks for chromosomal diseases is subject to considerable uncertainty, although it was used by the Committee in the UNSCEAR 1977 Report [U5]. However, there is definite evidence for the induction of structural chromosomal anomalies, particularly reciprocal translocations (but not Robertsonian translocations) in mammalian and human germ cells. With certain assumptions, the doubling dose method can therefore be used to estimate risks from the induction of at least certain kinds of structural chromosomal anomalies.

13. The estimation of risks associated with the induction of congenital anomalies and other diseases of complex aetiology (whose spontaneous prevalences are much higher than those of Mendelian and chromosomal diseases) poses a different problem. For a number of well-studied conditions belonging to this group, the evidence is consistent with the assumption that their aetiology is multifactorial, depending on polygenic genetic predisposition and environmental factors that may also be multiple. In order to be able to estimate risks of induction for this group of diseases, the BEIR Committee [B1] introduced the concept of "mutation component" in its 1972 Report (see also [C1] and [C2]). In that Report [B1], the mutation component of a disease was defined as "the proportion of its incidence that is directly proportional to the mutation rate". For Mendelian diseases and chromosomal anomalies, the mutation component is 1, except if there is some selective advantage in the heterozygote; for the diseases of complex aetiology mentioned above, it was assumed that this component is less than 1 (in the range 0.05-0.5). Therefore, for the estimation of risks of inducting this group of diseases, the principle is the same as that for autosomal dominant and X-linked ones, except that the product of p, 1/c and x (see paragraphs 7-9) is to be further multiplied by the mutation component.

14. In addition to the doubling dose method discussed above, a number of other methods, called direct methods, have been used over the years for the estimation of genetic risks; these are discussed later. The advantage of these methods is that they express absolute risks in terms of effects expected in the progeny for the different kinds of genetic damage on the basis of experimental data. However, it has not always been possible to bridge satisfactorily the gap between the estimates of rates of induction and the actual effects expected in terms of genetic disease.

I. BRIEF HISTORY OF THE APPROACHES TO GENETIC RISK ASSESSMENTS

A. THE DOUBLING DOSE METHOD

1. Reports by different scientific bodies, including UNSCEAR, in the period 1956-1966

15. The general radiation genetic principles that guided the BEAR Committee [B2], the British Medical Research Council Committee [M1] and UNSCEAR [U1] in the preparation of their respective reports in the mid- and late 1950s were those that emerged from the extensive work with Drosophila (primarily mature sperm irradiation), ongoing work with experimental mammals (primarily with the mouse) and the few sparse human data. Of these principles, the following deserve mention: (a) mutations, spontaneous or induced, are

usually harmful; (b) any dose of radiation, however small, entails some genetic risk; (c) the number of mutations produced is proportional to the dose, so that linear extrapolation from high-dose data provides a valid estimate of the low-dose effects; and (d) the effect is independent of the dose rate at which the radiation is delivered and of the spacing between the exposures.

16. In its 1956 Report, the BEAR Committee [B2] estimated that the doubling dose was probably between 30 R and 80 R and that it would be reasonable to use 40 R in computations. It also assumed that about 2% of all live-born children are, or will be, seriously affected by defects of "simple genetic origin". Under the further assumption that for this fraction of human genetic defects the incidence is proportional to the mutation rate, the effect at equilibrium after a continuing exposure to the then-recommended limit of 10 R per generation was computed. The conclusion was that there would be about 5,000 new instances of "tangible inherited defects" per million births, with about one tenth of this number in the first generation after the beginning of radiation exposure. The general philosophy, the range and the best estimates of the doubling dose arrived at by the British Medical Research Council Committee [M1] and by UNSCEAR [U1] were roughly similar.

17. With increasing reliance on mouse data, attention was focused on collecting more extensive information after irradiation of spermatogonia and oocytes, the cell stages most at risk from the standpoint of genetic risks. The results that became available (after the publication of the three reports mentioned earlier) demonstrated that (a) chronic gamma-irradiation of spermatogonia was mutationally less effective (by a factor of about 3) than the same total dose of high-dose-rate x-irradiation [R1, R3]; (b) following acute x-irradiation at high doses, the mutation rate in mature and maturing oocytes was higher than in spermatogonia; and (c) the dose-rate effect in females was even more pronounced than in males [R4].

18. On the basis of these results, the UNSCEAR 1962 Report [U2] suggested that for chronic low-LET irradiation of males, the doubling dose was probably 3-4 times the value of 30 R used in the UNSCEAR 1958 Report [U1] and also noted the possibility that, for similar radiation conditions, the doubling dose for females could be higher than for males. It was pointed out that ". . . a permanent doubling of the mutation rate would ultimately double the prevalence of those serious defects determined by the unconditionally harmful genes which are estimated to affect about 1% of those born alive".

19. By the time of the UNSCEAR 1966 Report [U3], the earlier mouse results had been amply confirmed and extended and new data had been obtained in females showing that there was a dramatic effect of the interval between irradiation and conception: in the first seven weeks after irradiation, the mutation frequency was high; subsequently, however, no mutations at all were recovered [R5]. In view of the wealth of mouse data that by then had accumulated, the Committee abandoned the doubling dose approach in favour of a more direct approach, using primarily the mouse specific-locus data as a basis. This aspect will be discussed later.

2. The UNSCEAR 1972 and BEIR 1972 Reports

20. In the UNSCEAR 1972 Report, the Committee revived its interest in the doubling dose method but gave it a low profile. Part of the reason for this renewed interest was that Lüning and Searle [L1] had summarized a number of estimates of doubling doses for different kinds of genetic damage in the mouse (semi-sterility, specific locus mutations, dominant visibles, mutations affecting the skeleton and autosomal recessive lethals). They all fell within a range of 16-51 R, averaging about 30 R for spermatogonia exposed to high acute x-ray doses. On the basis of the dose-rate studies on the induction of specific locus mutations in male mice, it was inferred that the doubling dose for chronic low-LET irradiation conditions could be about three times the above value, i.e., 100 R. Lüning and Searle [L1] gave no doubling dose estimates for females, since very little information on spontaneous rates was available in the literature.

21. On the assumption, based on the Northern Ireland survey [S1], that in man about 3% of live born are affected by deleterious traits maintained by mutation (now including simple dominants, some traits of uncertain genetic origin and chromosomal anomalies) and that the doubling dose is 100 R, UNSCEAR [U4] estimated that there would be about 300 extra cases per million live births for each rad of low-dose-rate, low-LET radiation to the males of the parental generation. It argued that ". . . the great majority of these will be (the result of) gene mutations with an unknown degree of dominance . . . if, however, the range observed in Drosophila (2-5%) is used as an upper limit to the average dominance in man as expressed by the frequency of deleterious traits among liveborn, then 6-15 affected individuals per million liveborn would be expected in the first generation following irradiation, the rest of the damage being expressed in subsequent generations".

22. In 1972, the BEIR Committee published its Report [B1]. In that Report, the doubling dose was calculated using an assumed range for the rate of spontaneous mutations in man ($0.5\ 10^{-6}$ to $0.5\ 10^{-5}$ per gene) and an induction rate from mouse specific-locus data ($0.25\ 10^{-7}$ per locus per rem, an average rate taking into account both sexes and assumed to apply to low-dose-rate, low-LET irradiation conditions). The range 20-200 rem thus derived represents a "hybrid" doubling dose range. On the basis of the Northern Ireland survey [S1] (as may be recalled, this was also the basis for UNSCEAR's figures), the BEIR Committee assumed that the prevalence of genetic diseases in the human population is about 6% (including 1% dominant and X-linked diseases, 1% chromosomal and recessive diseases and 4% congenital anomalies and other diseases of complex aetiology), and they estimated the effects of 5 rem per generation on a population of 1 million live births.

23. Further considerations or assumptions used in that exercise were the following: (a) since the incidence of dominant and X-linked traits is essentially proportional to the mutation rate, their frequency will be increased by the relative mutation risk per rem multiplied by the dose; (b) the incidence of recessive diseases is only very indirectly related to the mutation rate; (c) diseases caused by chromosomal anomalies are not likely to be very much increased by low-level irradiation; (d) for diseases of complex aetiology, the mutation component is likely to be in the range of 5-50% (see paragraph 13); (e) for dominant and X-linked diseases, the expected increase in the first generation is likely to be about 20% of that at equilibrium (based on the finding, in the Northern Ireland survey, that the population incidence was only four fifths of the incidence in new-borns, and this is roughly equivalent to assuming that the average mutant persists in the population for five generations); (f) for diseases of complex aetiology, the first-generation incidence will be about one tenth of that at equilibrium.

24. The estimated effect of 5 rem per generation on a population of 1 million live births was 300-7,500 new cases of genetic disease at equilibrium and 60-1,000 cases in the first generation, relative to the assumed prevalence of 60,000 cases of spontaneous origin per million live births. To facilitate comparisons with the other estimates, the recalculated figures for 1 rem per generation are summarized in Table 1.

3. The UNSCEAR 1977 Report

25. At the time of the preparation of the UNSCEAR 1977 Report [U5], the Committee had access to (a) detailed analyses of mouse data obtained after chronic gamma-ray exposures and estimates of doubling doses therefrom [S2, S3]; (b) the results of the continuing studies of mortality rates among children born to survivors of the atomic bombs in Hiroshima and Nagasaki, published by Neel et al. [N1]; and (c) new data on the prevalence of Mendelian and chromosomal diseases, as well as on the prevalence of diseases of complex aetiology, from an extensive survey carried out in the Canadian province of British Columbia and published by Trimble and Doughty [T1].

26. The estimates of doubling doses for the mouse for different genetic end-points fell in the range 80-249 R [S2, S3]. Analysis of the Japanese mortality data by Neel and colleagues showed no significant effects of parental exposure on the mortality of children through the first 17 years of life but suggested that the doubling dose for this kind of damage is about 46 rem for fathers and about 125 rem for mothers, for the acute radiation conditions that obtained during the bombings. Neel et al. suggested that, on the basis of mouse data, the gametic doubling dose for human beings would be expected to be 3-4 times the value of 46 rem for males and as much as 1,000 rem for females.

27. UNSCEAR examined both the mouse data and the Japanese data mentioned above and concluded that it would be prudent to continue to use the doubling dose of 100 R for estimating human radiation hazards. It also appraised the British Columbia prevalence figures, taking into account, among other things, the results of the Northern Ireland survey, of several *ad hoc* surveys for specific dominant conditions and of new-born surveys for chromosomal anomalies, as well as the uncertainties involved in the aetiology of the multifactorial diseases. The following figures (expressed per 10^6) that were arrived at were used for hazard evaluation: 10,000 dominant and X-linked diseases; 1,100 autosomal recessive diseases (excluding those maintained by heterozygous advantage of the relevant genes); 4,000 chromosomal diseases (including sex-chromosomal aneuploids, autosomal trisomies and unbalanced forms of translocations, but excluding mosaics and balanced structural rearrangements); and 90,000 diseases of complex aetiology—a total of 105,100 diseases per 10^6 live births.

28. Using a doubling dose of 100 rad and the prevalence figure of 105,100 per 10^6 mentioned above, UNSCEAR [U5] estimated that, if the population were continuously exposed to low-LET irradiation at a rate of 1 R per generation, there would be a total of about 185 cases of Mendelian, chromosomal and other diseases per million live births at equilibrium, of which about one third would be expressed in the first generation (0.17% versus 0.06%, respectively, of the assumed prevalence of 10.5%) (see Table 2). These figures were arrived at using the following assumptions: (a) for dominant and X-linked diseases, the first-generation increase will be about one fifth of that at equilibrium; (b) for recessive diseases, there will be no perceptible increase; (c) for chromosomal diseases, all those due to numerical anomalies and three fifths of those due to unbalanced structural rearrangements will be expressed in the first generation; and (d) the mutation component of diseases of complex aetiology is probably about 5%, and the first-generation increment in the frequency of these disorders is probably 10% of that at equilibrium.

4. The BEIR 1980 Report

29. Subsequently, the BEIR Committee published its 1980 Report [B3]. Its summary of risk assessments is reproduced in Table 3. It should be noted that (a) prevalence figures for Mendelian, chromosomal and other diseases are essentially the same as those used in the UNSCEAR 1977 Report; (b) the calculation of risks is based on an assumed doubling dose range of 50-250 rem (instead of 20-200 rem used in the BEIR 1972 Report); (c) the risks are expressed for a population exposure of 1 rem per generation (instead of the 5 rem per generation used earlier); and (d) whereas in 1972 the doubling dose method was the preferred method of expressing risks at equilibrium and in the first generation, in the 1980 Report only the equilibrium values were obtained using the doubling dose method (the first-generation values given in Table 3 were arrived at using a direct method, to be discussed later).

30. Concerning the new doubling dose range 50-250 rem used in the BEIR 1980 Report, the

Committee stated: "... this is based mainly on our best substantiated estimates of the doubling dose; namely, 114 R for mouse spermatogonia; we approximately halve and double this to get our range of 50 to 250 rem". Moreover, although a direct method was used to obtain first-generation figures, it is stated in the Report that such figures can also be arrived at using the equilibrium values (estimated using the doubling dose method) and making assumptions similar to those made in 1972 (namely, for dominant and X-linked diseases, the first generation increase will be one fifth of that at equilibrium and for disorders of complex aetiology about one tenth of that at equilibrium).

5. The ICRP Task Group 1980 Report

31. In 1980, Oftedal and Searle [O1] published the conclusions of a Task Group of ICRP on "genetic risk estimates for radiological protection". Their risk estimates are reproduced in Table 4. While the basic data and several of the assumptions used by the Task Group were similar to those used by UNSCEAR in 1977, the numerical estimates of risk by the former were different. The important differences pertain to risk estimates for diseases of complex aetiology and for diseases stemming from unbalanced products of induced balanced reciprocal translocations. These will now be considered in turn.

32. As may be recalled (paragraph 28), it was estimated in the UNSCEAR 1977 Report that the risk of induction of diseases of complex aetiology is a product of their prevalence (taken to be 90,000 per 10^6 live births, on the basis of the results of the British Columbia study); their average mutation component (assumed to be 5%); the relative mutation risk (estimated as 1/100 on the basis of the doubling dose estimate of 100 rad); and the dose sustained (assumed to be 1 rad per generation). The figure arrived at was 45 cases per 10^6 live births (i.e., $90{,}000 \times 1/100 \times 0.05$) at equilibrium. Under the assumption that the increase in the first generation would be about 10% of the above, the Committee derived a figure of 4.5 cases per 10^6 live births in the first-generation progeny.

33. The Task Group did not, however, use any prevalence figure for the above class of diseases to make risk estimates. Instead, (a) they split up the diseases of complex aetiology into (i) dominants of incomplete penetrance and multifactorial diseases maintained by mutation (i.e., those that respond to induced mutation) and (ii) multifactorial diseases not maintained by mutation (i.e., those that do not respond to induced mutation) and (b) they assumed that the expected increase in the frequency of group (i) above (as a result of radiation exposure to the population) is unlikely to exceed the sum of expected increments in Mendelian and chromosomal diseases; in the Task Group's calculations, this amounted to 160 cases per 10^6 live births at equilibrium. Thus, the estimate of 160 cases per 10^6 live births was arrived at in a way different from that used by UNSCEAR.

34. In the UNSCEAR 1977 Report the risk of production of unbalanced gametes leading to congenitally malformed children (stemming from the induction of balanced reciprocal translocations in males) on the basis of combined marmoset and human cytogenetic data. The estimate was 2-10 affected children per 10^6 live births in the first generation per rad of paternal irradiation. The lower limit of the above range was for chronic gamma-irradiation and the upper limit was for low-dose-rate x-irradiation. The risk for the irradiation of females was considered to be low, but no quantitative estimates were given.

35. The Task Group's estimate for the above class of genetic damage was 30 cases per 10^6 live births per rad of parental (i.e., both sexes) irradiation with low-dose-rate x rays and was based on the same set of marmoset and human cytogenetic data. However, the Task Group assumed that the risk from translocation induction would be the same in both sexes (whereas UNSCEAR assumed that it would be lower in females).

6. The UNSCEAR 1982 Report

36. The risk estimates of the UNSCEAR 1982 Report [U6] are reproduced in Table 5. They are basically the same as those derived in the UNSCEAR 1977 Report [U5], except for two changes: (a) for dominant and X-linked diseases, the first-generation increment was assumed (in 1982) to be 15% of that at equilibrium (instead of the 20% assumed in 1977), based on the calculations of Childs [C3], and (b) diseases due to chromosomal anomalies were split up into those due to numerical anomalies and those due to structural anomalies; it was assumed that the increase due to the induction of numerical anomalies would probably be quite small and that the first-generation increment of those due to structural anomalies would be about three fifths of that at equilibrium. Consequently, the expected total increases at equilibrium (~150 cases per million live births) and in the first generation (~22 cases per million live births) are lower than the corresponding values estimated in 1977 (185 and 63 cases, respectively).

37. It is worth pointing out that at the time the UNSCEAR 1982 Report was prepared, the Committee had at its disposal the papers of Neel et al. [N2] and Schull et al. [S4, S5]. They contained an analysis of all the available genetic data obtained in the continuing studies of the Hiroshima and Nagasaki populations (a follow-up of the material presented by Neel and colleagues in 1974 [N2]). These new data pertained to untoward pregnancy outcomes (i.e., those resulting in children with major congenital defects, still births and deaths in the neonatal period), survival through childhood, incidence of sex-chromosomal anomalies and incidence of biochemical variants (erythrocyte and plasma protein variants, analysed using one-dimensional electrophoresis). In all the calculations, the T65D dosimetry was used and an RBE of 5 for neutrons was assumed. As Schull et al. [S5] pointed out, "... in no instance was there a statistically significant effect of parental exposure ... but for all indicators, the observed effect was in the direction suggested by the hypothesis that genetic damage resulted from the exposure."

38. Doubling dose estimates were made only for the first three indicator traits since the data on biochemical variants were considered too preliminary. The gametic doubling dose estimates presented by Schull et al. [S5] were the following: untoward pregnancy outcomes, (69 ± 93 rem); survival through childhood (F_1 mortality), (171±388 rem); and sex-chromosomal aneuploids, (535 ± 2,416 rem). The weighted average of these estimates is (139 ± 157 rem). Schull et al. [S4] considered that the doubling dose estimate for low doses and low dose rates might be higher by a factor of 3.

39. The main message from these papers is that the doubling dose for human genetic effects may be about 4 Gy, i.e., about four times the value used by UNSCEAR, which would mean that the relative risks estimated by UNSCEAR are too high by a factor of 4. The Committee examined these data and the analysis presented and concluded that, in view of the lack of statistically significant effects and the high standard deviations associated with the doubling dose estimates, it would be premature to use these results for genetic risk assessments at the present time. Therefore, the earlier doubling dose estimate of 1 Gy (based entirely on mouse data) was retained.

7. The NUREG 1985 Report

40. In 1985, a report prepared for the U.S. Nuclear Regulatory Commission entitled "Health effects model for nuclear power plant accident consequence analysis" was published [E7]. This report, hereinafter to be referred to as the NUREG Report, included (among other things) estimates of genetic risk arrived at by the doubling dose method for low-dose-rate, low-dose, low-LET irradiation conditions. Important aspects of these estimates are the following: (a) the basic data on the prevalence of autosomal dominant and X-linked diseases and of irregularly inherited diseases are the same as those used by UNSCEAR in 1982 and by the BEIR Committee in 1980; (b) the doubling dose used is 1 Gy (the same as UNSCEAR used in 1982 but different from the 50-250 rem range used by the BEIR Committee in 1980); (c) the mutation component of irregularly inherited diseases was taken to be in the range 0.05-0.5 (the same as in the BEIR 1980 Report, but different from the value of 0.05 used by UNSCEAR in 1982); (d) the risk estimates were made for a total population of 10^6 persons with 16,000 live births per year (or 480,000 in a 30-year generation), based on 1978 demographic data from the United States (UNSCEAR's estimates were for a population of 10^6 live births); and (e) estimates of risk for the first generation were derived not from the equilibrium values but by using a direct method (UNSCEAR's estimates were derived from equilibrium values as well as by using a direct method). The relevant table from the NUREG Report is reproduced here as Table 6.

8. The UNSCEAR 1986 Report

41. The risks estimated by the Committee in the UNSCEAR 1986 Report (with some additions) are given in Table 7. The additions pertain to risk from recessive diseases and for second generation effects (see footnotes c, e and f of Table 7). It can be seen that (a) the estimates of prevalence and of risk for Mendelian and chromosomal diseases are the same as those used in 1982 and (b) no risk estimates are provided for diseases of complex aetiology (i.e., for congenital anomalies and other multifactorial diseases), although they had been provided in 1982. The reasons for this departure are set out below.

42. New data on diseases of complex aetiology that became available subsequent to the UNSCEAR 1982 Report provided grounds for believing that their prevalences may need upward revision. First, the compilation and analysis of the extensive results on congenital anomalies in the Hungarian population [C5] suggested that their prevalence is about 60,000 per 10^6 live births (compared with 43,000 per 10^6, based on the British Columbia study and used in the UNSCEAR 1977 and 1982 Reports); on the basis of their aetiology, the congenital anomalies can be roughly subdivided into those due to major genes (6% of the total of 60,000 per 10^6); multifactorial causation (50% of the total); chromosomal anomalies (about 5% of the total); environmental, including maternal, factors (about 6% of the total); and aetiology as yet unknown (the remaining 30%, approximately, of the total) (see UNSCEAR 1986 Report, Annex C, paragraphs 51-58).

43. Second, in the same population, the prevalence of other irregularly inherited diseases, most of them of late onset (in middle age and later), was estimated to be about 600,000 per 10^6 of the population (see UNSCEAR 1986 Report for a discussion of these data). Relative to the prevalence used in the UNSCEAR 1977 and 1982 Reports (47,000 per 10^6 live births, based on the British Columbia study), the Hungarian prevalence for these diseases is at least an order of magnitude higher. One must hasten to add, however, that (a) the British Columbia figure relates to those multifactorial diseases with onset before the age of 21, whereas the Hungarian figure pertains to lifetime (taken as 70 years) prevalence, and (b) in Hungary, the actual frequency of affected individuals will be fewer than 600,000 per 10^6 because many of them will suffer from more than one of these diseases. One further point relates to the fact that the diseases included in the Hungarian list (at least 25 entities[a]) are by no means homogeneous, either clinically or aetiologically; the same is true of those included in the British Columbia list.

44. During the preparation of the UNSCEAR 1986 Report, the Committee discussed at length these data, the question of a new risk estimate for these diseases and the appropriateness of the assumptions used earlier (i.e., a doubling dose of 1 Gy, a mutation

[a] Thyrotoxicosis, diabetes mellitus, gout, schizophrenia, affective psychoses, multiple sclerosis, epilepsy, glaucoma, essential hypertension, acute and sub-acute myocardial infarction, varicose veins, allergic rhinitis, asthma, gastric ulcers, idiopathic proctocolitis, cholelithiasis, calculus of kidney and ureter, atopic dermatitis and related conditions, psoriasis and related conditions, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, juvenile osteochondrosis of the spine and adolescent idiopathic scoliosis.

component of 5% and 10% expression in the first generation). If these assumptions were valid (which seem very doubtful), then, the estimate would be 330 cases of diseases of complex aetiology per 10^6 at equilibrium (i.e., $660{,}000 \times 1/100 \times 0.05 = 330$) under conditions of continuous irradiation at a rate of 0.01 Gy per generation. The expected increases in the first and second generations would then be, 33 and 30 cases, respectively, per 10^6. These estimates are about sevenfold higher relative to those arrived at in 1977 and 1982, on the basis of a prevalence figure of 90,000 per 10^6. Although there is no reason to believe that the actual risk from these diseases would be less than those arrived at in 1977 and 1982, there are at least three reasons why the reliability of the estimates based on the prevalence of 660,000 per 10^6 is open to question: (a) the prevalence figure of 600,000 per 10^6 for multifactorial diseases refers to the number of diseases per 10^6 of the population rather than to the actual number of affected individuals; it also includes conditions of less severity such as allergic rhinitis and psoriasis; (b) the applicability of the doubling dose of 1 Gy (which is based entirely on mouse results for clearly defined genetic end-points) to diseases of complex aetiology remains questionable in the absence of information on the mechanisms of maintenance of these diseases in the population and what effect, if any, radiation would have on their prevalence; and (c) the assumption of a 5% mutation component for the diseases included in the new data-set cannot be scientifically defended in the absence of a systematic analysis. These considerations led the Committee to express the view that it is at present unable to provide a reliable estimate of risk for these diseases. However, there is some hope (see paragraphs 90-91) that the difficulties will be at least partially resolved in the not too distance future.

9. The doubling dose method in retrospect

45. The rationale for the continued use of the doubling dose method for risk evaluation is that it permits one to express risks in tangible terms and that whole classes of genetic effects can be handled as a unit in the absence of information about, for instance, the number of loci involved or their individual mutation rates. The early estimates of doubling doses fell in the range 10-100 R (then, for acute, high-dose-rate irradiation), and the possible representative values lay between 30 and 40 R. With the discovery, in 1962, of dose-rate effects in the mouse, UNSCEAR adopted 1 Gy as the best estimate, and this value is still being used. However, (a) individual estimates for different kinds of genetic damage vary from about 0.8 to 2.4 Gy in the mouse and (b) the analysis of the Hiroshima and Nagasaki data suggests that the value may be higher than 1 Gy. The principal reasons for adhering to the 1 Gy estimate are that the human evidence is far from conclusive and that caution and prudence are the guiding principles in this endeavour. The changes in the estimates of relative risks from the mid-1950s to the present thus reflect increasing knowledge on the prevalence of these diseases in the human population and the evolving assumptions on their possible responses to an increase in mutation rate and not any real breakthrough in the understanding of the genetic sensitivity of human germ cells to ionizing radiation.

B. THE DIRECT METHODS

1. Direct methods used between 1956 and 1972

46. Some of the basic radiation genetic principles that guided the BEAR Committee [B2] as it prepared its 1956 Report were briefly alluded to earlier. In addition, advances in radiation genetics and in theoretical and experimental population genetics had even by that time documented the thesis that the changes due to mutated genes are seldom fully expressed in the first-generation progeny of irradiated individuals and that these mutant genes persist in the population for shorter or longer periods of time, depending on their deleterious effects on fitness, until they are eventually eliminated from the population. The concept of genetic death enunciated by Muller [M2] was current and influenced much of the thinking of geneticists. It seemed logical, therefore, to apply the concept to the estimation of genetic risks. This point of view was succinctly stated by the BEAR Committee [B2] as follows: "One way of thinking about this problem of genetic damage is to assume that all kinds of mutations on the average produced equivalent damage, whether as a drastic effect on one individual who leaves no descendants because of this damage, or a wider effect on many. Under this view, the total damage is measured by the number of mutations induced by a given increase in radiation, this number is to be multiplied in one's mind by the average damage from a typical mutation."

47. It was thought, therefore, that the total risk due to induced mutations could be obtained as the product of three factors (i.e., the number of genes at which mutations can occur, the radiation dose and the rate per gene per unit dose) and that the expression of this risk in the first and succeeding generations could be estimated by population genetic methods. Some limited data were available on mutation rates in mice; the main difficulty was the lack of reliable gene numbers for humans. To circumvent this problem, the BEAR Committee used Drosophila data, dividing the total mutation rate (for recessive lethals per gamete) by that for individual genes, multiplied this ratio by 2 to 3 to allow for mutations with less-than-lethal effects and arrived at a figure of about 10^4; this figure was then used along with the mutation rate inferred from mouse studies to estimate the "total number of mutant genes that would enter the population in the next generation if everyone in the United States of America received a dose of 10 R to the reproductive glands" ($5\ 10^6$ mutant genes) [B2]. It is thus clear that this estimate was for "a hypothetical organism whose mutation rate per gene is that of the mouse and whose gene number is that of Drosophila" (see [B1] for a discussion). The BEAR Committee concluded, however, that ". . . this kind of estimate is not a meaningful one to certain geneticists . . . their principal reservation is doubtless a feeling that, hard as it is to estimate the number of mutants, it is much harder still, at the

present state of knowledge, to translate this over into a recognizable statement of harm to individual persons" [B1]. The method was then abandoned [B1, B3].

48. In its first Report of 1968, UNSCEAR did not use any direct methods. In 1966, it used a variation of the method used by the BEAR Committee. It was argued that (a) if it is assumed that the average rate of induction of recessive mutations in the mouse (estimated as $1\ 10^{-7}$ per locus per R from data obtained for specific locus mutations, following high-dose, high-dose-rate x-irradiation of spermatogonia) is applicable to man and (b) if, for the purpose of computation, the total number of gene loci in man were assumed to be 20,000 (range: 7,000-70,000), then the total risk from the induction of point mutations will be $2\ 10^{-3}$ mutations per gamete per R. This estimate was higher than the one arrived at using the limited data on the induction of autosomal recessive lethals in mouse spermatogonia as a basis ($0.5\ 10^{-3}$ mutations per gamete per R), although not significantly so. The expression of this risk in the first and succeeding generations was then estimated using the average degree of semi-dominance of recessive lethals in Drosophila.

49. For estimating more directly the risk from the induction of dominant mutations, the Committee assumed that the rate is likely to be from 10^{-9} to 10^{-7} per locus per R and that the number of loci determining dominant diseases in man ranges from 50 to 500. The total risk was thus estimated to be from $5\ 10^{-8}$ to $5\ 10^{-5}$ mutations per gamete per R. Similar estimates of risk from the induction of chromosomal aberrations (translocations and deletions) were arrived at using the limited data on the induction of heritable semi-sterility in the mouse and data on the induction of dicentrics and deletions in human peripheral blood lymphocytes. It was pointed out that all the risks would be lower for chronic irradiation conditions.

50. In the UNSCEAR 1972 Report [U4], the Committee approached the problem of estimating gene numbers in the following way. In the mouse, there are about 20 functional units per cross-over unit [R6] and there are some 1,250 map units in the entire genome [G1]. This gives about 25,000 functional units in the mouse genome. The DNA of the mouse and human diploid genomes were estimated to contain $4.7\ 10^9$ and $5.6\ 10^9$ nucleotide pairs, respectively. Thus the estimate of the total number of functional units in the human genome was $25{,}000 \times (5.6/4.7) = 30{,}000$. By assuming that the rate of induction of specific locus mutations in mouse spermatogonia under conditions of chronic gamma-ray exposure ($0.5\ 10^{-7}$ per locus per rad; average estimate based on the 12 loci studied) was applicable to man, the total risk from the induction of point mutations in man was estimated to be 1,500 mutations per rad per million gametes (i.e., $0.5\ 10^{-7} \times 30{,}000$) (Table 8). This was considered an overestimate, because specific locus mutations may involve more than one functional unit.

51. The estimate of total risk based on the new mouse data (discussed in the 1972 Report) on the induction of autosomal recessive lethals (spermatogonial irradiation), after correction for DNA content, was 36 mutations per rad per million gametes, and this was considered a possible underestimate. The first-generation expression of these risks (computed using, as before, the degree of semi-dominance of recessive lethals (2-5%) inferred from Drosophila studies in conjunction with the total rate of 1,500) amounted to 36 mutations per rad per million gametes.

52. A modified version of the gene number approach was also used in the UNSCEAR 1972 Report for estimating the rate of induction of dominant mutations in man. For this purpose, the rate of induction of dominant visible mutations in mouse spermatogonia ($4.96\ 10^{-7}$ per rad per gamete) was used. Since this rate was for acute, high-dose-rate x-irradiation, it was divided by 3 to correct for effects at low dose rates and divided by 75 (the then-presumed number of loci in the mouse that mutated to dominant visibles), giving a rate of $2.2\ 10^{-9}$ per locus per gamete per rad.

53. The 1971 compendium of McKusick [M3] listed 415 autosomal dominant loci in man plus another 528 for which the evidence was inconclusive. Assuming that there was "good reason to predict that the number will not be less than 1,000 based on progress of research in this area", the Committee multiplied $2.2\ 10^{-9}$ by 1,000 and obtained an estimate of about two dominant mutations per rad per million gametes [U4].

54. In its 1972 Report, UNSCEAR also provided an estimate of risk from the induction of reciprocal translocations in man, using a direct method. This was done by assuming that (a) the rate of induction of balanced reciprocal translocations in man would be twice that in mouse germ cells (i.e., $2 \times 0.3\ 10^{-4}$ per gamete per rad, based on the arm number hypothesis of Brewen et al. [B4], which was then, but is not now, considered valid); (b) at low doses or low dose rates, the rates in males would be reduced by factors of 4 or 7, respectively; (c) the ratio of balanced to unbalanced products would be 1:2; and (d) only about 6% of the unbalanced products would result in liveborn children with multiple congenital anomalies. Taking all these assumptions into account, it was estimated that the risk was 1-2 congenitally malformed progeny per million live born, following irradiation of males. (It is worth mentioning that in its 1972 Report, the BEIR Committee also provided an estimate of risk from the induction of reciprocal translocations; using the same basic data and a different set of assumptions, it arrived at an estimate that was an order of magnitude higher than the estimate of UNSCEAR.)

55. In retrospect, despite gallant efforts to weld the principles of population genetics, the concept of genetic death and the principles of radiation genetics in order to arrive at risk estimates for the induction of mutations, the hopes that, until 1972, had been raised by the gene number method proved illusory. Apart from the difficulties of reliably estimating gene numbers, the conceptual difficulties of bridging the gap between the dynamics of mutant genes in the population, on the one hand, and genetic disease, on the

other, were so numerous that the method fell short of expectations and faded into oblivion. Furthermore, the degree of semi-dominance of recessive mutant genes, used to extract first-generation effects from the total risks, referred in reality to the effects of these genes on biological (reproductive) fitness and not to genetic diseases as such.

2. The UNSCEAR 1977 and BEIR 1980 Reports

56. In the UNSCEAR 1977 Report, a major conceptual change was introduced. At the time of preparation of the above Report, the Committee had at its disposal the earlier data collected by Ehling [E1, E2] on the induction of dominant mutations affecting the skeleton of the progeny of irradiated male mice and the new data on these collected by Selby and Selby [S7]. The data of the latter authors established that these skeletal mutations were in fact transmissible and also showed that they had incomplete penetrance and variable expressivity for many or all of the phenotypic effects they caused and, besides, that some of them behaved as recessive lethals when made homozygous. Doubtless, some of the properties of these mutations are similar to those of rare dominants and rare, irregularly inherited dominants in man.

57. However, in order to convert the rate of induction of mutations causing skeletal abnormalities in the mouse into an overall rate for all mutations with dominant phenotypic effects in man, information is needed on (a) the proportion of dominant conditions in man whose main effect is in the skeleton and (b) the proportion of skeletal abnormalities studied in the mouse that, at the human level, is likely to cause a serious handicap. After careful deliberation, UNSCEAR arrived at values of 10% for item (a), taking into account the proportion of clinically relevant autosomal dominants in man whose main effect is in the skeleton (which was assessed at 20%) and the ease of diagnosis of skeletal defects (possibly higher by a factor of 2) relative to defects in other bodily systems. The proportion of skeletal anomalies in the mouse that might cause a serious handicap (item (b) above) should they occur in man, was assessed as one half.

58. In risk estimation, the frequency of skeletal mutations observed after high fractionated or high acute x- or gamma-ray doses was corrected by suitable factors to arrive at a rate that would be applicable for low-dose-rate, low-LET irradiation conditions. The resultant rate of $4\ 10^{-6}$ was multiplied by 10 and divided by 2, to give $20\ 10^{-6}$, which is the probability of induction of mutations causing dominant effects in any of the bodily systems in man. In other words, following 1 R of paternal (spermatogonial) irradiation, 20 per million progeny would carry mutations causing one or another kind of dominant genetic disease, in the first generation (see Table 9).

59. In its 1980 Report, the BEIR Committee, starting from the same data-base as that used by UNSCEAR, gave a different estimate (5-65 cases per million per rem; see Table 3). There are two reasons for this difference. First, to convert the rate of induction of skeletal mutations in mice to an overall rate involving all bodily systems in human beings, UNSCEAR used a factor of 10, as mentioned in the preceding paragraph; this was divided by 2 to exclude mutations whose effects were slight.

60. The BEIR Committee, by contrast, multiplied by 5-15 to make the first conversion and multiplied by 0.25-0.75 to make the second conversion: these operations gave the range of 5-45 cases per million births. Second, to take into account the effects of irradiation of females, the BEIR Committee multiplied the upper limit by 1.44 (the UNSCEAR 1977 Report assumed that the risk for irradiated human females would be negligible and did not give any quantitative estimate). The rationale for the multiplication by 1.44 was stated as follows: "The mutational response of the resting oocytes in mice is negligible, compared with that of spermatogonia, and mature and maturing oocytes in mice have a mutation rate no greater than 0.44 times that found in spermatogonia. We do not know which of the two classes of oocytes would have a mutational response more similar to that of the arrested oocytes in women. To incorporate this range of uncertainty into our risk estimate for the combined effects of irradiation of both sexes, we have simply kept the lower limit of our estimate the same as it was (assuming a negligible mutation frequency in resting oocytes) and multiplied the upper limit by 1.44 (assuming the maximal estimate of the mutation frequency in mature and maturing oocytes). This gives an estimate of 5-65 induced serious disorders per million liveborn as the first generation expression. . . ."

61. In 1977, as may be recalled, using marmoset and human cytogenetic data [B5] as the basis for estimating the risk from the induction of reciprocal translocations, UNSCEAR arrived at an estimate of between 2 and 10 congenitally malformed children per million births per rad of low-LET irradiation of males. Briefly, the calculations were the following: $7\ 10^{-4}$ (rate of translocation induction; spermatocyte data) $\times$ 0.25 (factor to get the rate for heritable translocations in the progeny) $\times$ 0.1 or 0.5 (factors to account for dose-rate effect after chronic gamma-rays and low-dose x rays, respectively) $\times$ 2 (factor to estimate the rate of production of unbalanced products of reciprocal translocations) $\times$ 6% (the proportion of unbalanced products that was assumed to give rise to viable, but congenitally malformed, progeny). The risk for the irradiation of human females was considered to be small, but no quantitative estimate was given.

62. In its 1980 Report, the BEIR Committee used the marmoset cytogenetic data for estimating the risk associated with the induction of balanced reciprocal translocations in human males. Its estimate was $0.5\text{-}5\ 10^{-6}$ per rem (compared to that of UNSCEAR, $2\text{-}10\ 10^{-6}$ per rad, as reported in the preceding paragraph). The BEIR Committee's procedure was the following:

(a)	Basic rate	$7.7\ 10^{-4}$e/m/spermatocyte (marmoset cytogenetic data)
(b)	Rate of potentially transmissible rearrangements	$4.7\ 10^{-4}$e/m (multiply (a) by 2/3)

(c)	Correction for low total doses and for low dose rate	$2.3\ 10^{-4}$e/m (multiply (b) by 0.5)
(d)	Correction for the probability of adjacent segregations (unbalanced gametes)	$1.3\ 10^{-4}$e/m (multiply (c) by 0.55)
(e)	Correction for proportion of unbalanced gametes that would result in congenitally malformed live births	$6.5\ 10^{-6}$e/m (multiply (d) by 0.05)
(f)	Correction for the probability that only one of the four kinds of aneuploid segregation products will be viable in zygotes	$1.6\ 10^{-6}$e/m (multiply (e) by 0.25)
(g)	Correction for uncertainty	$0.5\text{-}5\ 10^{-6}$e/m (multiply (f) by 0.3-3)

63. For estimating risks for irradiated human females, the BEIR Committee made the same assumption as in its 1972 Report; namely, that the risk would be the same as that in males. Thus "the expected frequency of viable aneuploids for both sexes is assumed to range from $1\ 10^{-6}$ to $10\ 10^{-6}$ per rem". The BEIR Committee also used "an alternative and independent approach based on litter-size reduction observed after acute irradiation of mouse germ cells" and pointed out that "the upper limit of $10\ 10^{-6}$ for both sexes combined may be an overestimate, and that the true value could indeed be near to zero".

3. The UNSCEAR 1982 Report

64. The estimates of risk arrived at in the UNSCEAR 1982 Report are given in Table 10. They are basically the same as those arrived at in 1977, except for the following additions or changes: (a) an additional and independent estimate of risk from the induction of mutations having dominant effects in the F_1 progeny was presented, using the new data on the induction of dominant cataract mutations in male mice following spermatogonial irradiation; (b) the probable magnitude of risk for irradiation of females was arrived at very indirectly by assuming, on the basis of specific locus data, that the rate in females is likely to be either close to zero (on the assumption that the mutational sensitivity of the human immature oocytes may be similar to that of the mouse immature oocytes) or not more than 44% of the spermatogonial rate (see [R7]); and (c) for estimating risks from the induction of reciprocal translocations, all the then-available primate data (i.e., the marmoset data, the rhesus monkey data and the limited human data) were used.

65. The mouse cataract mutation data were obtained in experiments involving high acute or fractionated gamma-ray exposure [E3, E4, K1]. From these results, a rate applicable to chronic gamma-ray exposure was derived, using empirical correction factors derived from specific locus studies. This rate was about $2.6\ 10^{-7}$ per gamete per rad. In man, about 2.7% of all known and proven dominant mutations are associated with one or another form of cataract. The reciprocal of this (i.e., 100/2.7 = 36.8) was used as a factor by which to multiply the rate of $2.6\ 10^{-7}$, to arrive at approximately 10×10^{-6} per rad. In other words, for every rad of low-dose-rate, low-LET irradiation, about 10 individuals per million born will be affected by one or another kind of serious, clinically important, genetic disease. It is worth pointing out that these calculations did not use either the multiplier of 2 or the divisor of 2 that had been used in analogous computations with skeletal mutations to account for ease of diagnosis and severity of effects, respectively.

66. The extensive cytogenetic data on translocation induction in male rhesus monkeys show that the rate of induction, at least for high-dose-rate x-irradiation conditions, is much lower than that in marmosets ($0.86\ 10^{-4}$ versus $7.7\ 10^{-4}$ per rad per gamete) (see [B6]). Since it is not known whether human spermatogonial sensitivity is more like that of the marmoset or that of the rhesus monkey, the rates for both these species were used, one to define the probable upper limit of risk and the other, the lower limit. The correction factors used to convert the rhesus monkey acute rate into the rate applicable to human radiation conditions are the same as those used in the 1977 Report. Other correction factors and the underlying assumptions are explained in the footnotes to Table 10.

4. The NUREG 1985 Report and other publications

67. The direct estimates of risk presented in the NUREG Report [E7] (Table 6) differ in some respects from those in the BEIR 1980 Report. First, the NUREG Report assumes that both sexes have the same sensitivity to the induction of dominant mutations (the BEIR Committee assumed that the sensitivity of females is no more than 0.44 times that of males). The consequence of this assumption is that for irradiation of both sexes, the risk of induction of dominant genetic disease is twice that estimated for exposure of males; namely, $2 \times (5\text{-}45)\ 10^{-6}$ per 0.01 Gy, or $10\text{-}90\ 10^{-6}$ per 0.01 Gy. The geometric mean of this range (central estimate) is 30. As may be recalled (paragraph 60), the BEIR Committee multiplied the upper limit of the range 5-45 by 1.44 and came up with the range $5\text{-}65\ 10^{-6}$ per 0.01 Gy for irradiation of both sexes.

68. Second, the NUREG Report employed the gene number method (which is no longer used by either UNSCEAR or the BEIR Committee) to arrive at a risk estimate for X-linked genetic diseases. Assuming that the rate of specific locus mutations in male mice ($7.2\ 10^{-8}$ per locus per 0.01 Gy) is applicable for X-linked mutations as well, and that the number of loci in man at which X-linked mutations occur is 250, an estimate of $1.8\ 10^{-5}$ per 0.01 Gy was obtained for irradiation of males or females.

69. To obtain a "single central estimate" for induced translocations and the unbalanced segregation products, some of which produce viable but seriously affected live born, the NUREG Report used the following calculations:

(a)	Basic rate	$7.4\ 10^{-4}$/.01 Gy/spermatocyte (marmoset cytogenetic data)

(b)	Correction for low-dose-rate x rays	$3.7\ 10^{-4}$/.01 Gy/spermatocyte (multiply (a) by 0.5)
(c)	Correction of gamma-ray RBE	$1.48\ 10^{-4}$/.01 Gy/spermatocyte (multiply (b) by 0.4)
(d)	Correction for expected frequency of unbalanced products	$0.74\ 10^{-4}$/.01 Gy (multiply (c) by 0.5)
(e)	Correction for proportion of viable unbalanced products	$0.74\ 10^{-6}$/.01 Gy (multiply (d) by 0.01)

For irradiation of females, the rate was assumed to be the same as that in males (i.e., $1.48\ 10^{-4}$ per 0.01 Gy), and since the oocyte will contain the reciprocal translocation distributed between two tetrads of chromatids, the probability of recovering unbalanced products was estimated as nine sixteenths of the above; namely, $5.6\ 10^{-5}$ per 0.01 Gy. Assuming further that about one tenth of this would lead to viable aneuploids, it was estimated that the risk for irradiation of human females would be $5.6\ 10^{-6}$ per 0.01 Gy; for irradiation of both sexes, therefore, the total risk from induced translocations would be about 13 cases of abnormal progeny per million live births per 0.01 Gy of parental irradiation.

70. In addition to risk estimates for low-dose, low-dose-rate, low-LET irradiation conditions, the NUREG Report also provided estimates of genetic risk for the irradiation conditions that would prevail in nuclear accidents. As would be expected, the risks are higher under the latter conditions, but this case will not be further considered here.

71. The NUREG Report also sought to determine whether its risk estimates were consistent with the lack of detectable genetic effects of radiation in the genetic studies of Hiroshima and Nagasaki. In its analysis of the Japanese data, it used (a) the paper of Schull et al. as a basis [S13; specifically, Table 7, in which mortality up to age 17 for 16,173 children of exposed parents is correlated with the distribution of parental doses]; (b) the linear-quadratic model as the one applicable for the induction of gene mutations and chromosomal aberrations at high doses and high dose rates (developed independently of the Japanese data, on the basis of the experimental results discussed in the preceding paragraph); and (c) average doses for each exposure group (parents), i.e., 0.05 Gy (0.01-0.09 Gy); 0.295 Gy (0.10-0.49 Gy); 0.745 Gy (0.50-0.99 Gy); and 2 Gy (>1 Gy). These values were introduced into the equations to project the number of cases of each genetic event relative to the child sample size in each of the 32 sectors of exposure in the matrix of Schull et al. [S13].

72. The important conclusion that emerged from this analysis was that "the central estimate of prediction of cases should lead to a statistically insignificant, i.e., undetectable increase in genetic disorders among the 16,713 progeny of irradiated parents. For example, there were 1,040 deaths in this group of 16,713 progeny up to the age of 17 (6.22%); in the unexposed groups, there were 2,191 deaths among 33,976 progeny produced (6.45%) and the two frequencies are not significantly different, nor would they have been even if 50 additional cases were added to the exposed group [E7]."

73. Abrahamson [A2] and Ehling [E8] independently reached similar conclusions. In his analysis, Ehling used the estimate of the genetically significant dose (sustained by the survivors of Hiroshima and Nagasaki) of $1.1\ 10^{4}$ man Sv arrived at by WHO in its report entitled "The effects of nuclear war on health and health services" [W1]. The projected increases among the 19,000 children in the sample were less than one dominant cataract mutation and about 11 dominant skeletal mutations; the total number of expected dominant mutations was estimated to be 20-25 (on the basis of mouse cataract data) or about 56 (on the basis of mouse skeletal data). Ehling argued that, given the kinds of end-points used in the Japanese studies, (a) it is not surprising that no clear-cut positive evidence for the induction of genetic damage could be obtained and (b) the Japanese results are not inconsistent with the expectations based on the dominant cataract and skeletal data.

5. The UNSCEAR 1986 Report

74. The most recent estimates of risk, those of the UNSCEAR 1986 Report, are given in Table 11. The changes with respect to the estimates of 1982 are the following. First, on the basis of litter-size reductions observed in mouse studies involving acute, high-dose-rate x-irradiation, chronic gamma-irradiation or chronic fission neutron irradiation (in all, spermatogonial irradiation; these data are discussed in the 1986 Report), the Committee estimated that, following irradiation of male mice, between 5 and 10 per 10^{-2} Gy per million live born (in the first generation) would die between birth and weaning as a consequence of induction of dominant sub-lethal effects. In view of the uncertainty as to whether and to what extent litter-size reduction in mice can be extrapolated to mortality in humans between birth and early childhood, the above estimate has been appended to Table 11 as footnote b.

75. The second change (see footnote e in Table 11) pertains to the risk of induction of autosomal recessive genetic disease as a result of radiation exposures. In the past, the Committee's view has been that although recessive mutations are expected to be induced, no cases of individuals affected with recessive disease will occur in the first generation; it therefore made no attempt to present a quantitative estimate of risk in the subsequent generations following one-time or generation-after-generation radiation exposure. Searle and Edwards [S9] have now provided a numerical estimate of risk for autosomal recessive disorders. Basing their calculations on a combination of data from observations in human populations and in mice, these authors have estimated that (a) a genetically significant dose of 10^{-2} Gy of x- or gamma-irradiation received by each parent once in a stable population with 1 million live born would induce up to 1,200 additional recessive mutations; (b) from partnership effects (i.e., partnership with another recessive mutation

either induced or already present in the population), about one extra case of recessive disease would be expected in the following 10 generations; (c) homozygosity resulting from identity by descent would not normally occur until the fourth generation after exposure, but on certain assumptions, about 10 extra cases would be expected from this cause by the tenth generation; and (d) in the same period, about 250 recessive alleles would be eliminated as heterozygotes, on the assumption of a 2.5% heterozygous disadvantage. Such elimination through heterozygotes may occur through, for example, an increase in disease susceptibilities, malignancy or a decrease in intellect.

76. The third change pertains to risks associated with the induction of balanced reciprocal translocations. In its 1982 Report, the Committee used the cytogenetic data collected in studies with the rhesus monkey and the marmoset Saguinus fuscicollis, as well as some limited human data, as a basis for its risk estimates. The rates of unbalanced products of reciprocal translocations expected to be generated (estimated from the corresponding rates for balanced reciprocal translocations) were used in conjunction with the assumption that 6% of unbalanced zygotes might result in congenitally malformed children, giving the range 0.3-10 per 10^{-2} Gy per 10^6 live births (the lower limit was based on the rhesus monkey data and the upper one on the combined marmoset and human data). New data at low doses and low dose rates have since then become available from experiments involving the rhesus monkey and the crab-eating monkey; further, the estimate of conceptions with unbalanced products that may survive birth has been revised upwards, from 6% to 9% (discussed in the UNSCEAR 1986 Report). As a result, the estimated risk is now 1-15 cases of congenitally malformed children per 10^6 live births per 10^{-2} Gy of paternal irradiation and 0-5 cases per 10^6 live births per 10^{-2} Gy of maternal irradiation. Further details are given in footnotes f and g to Table 11.

II. RELEVANT NEW HUMAN DATA PUBLISHED AFTER THE UNSCEAR 1986 REPORT

77. The most recent results from the Hiroshima and Nagasaki genetic and cytogenetic studies again show no significant effects of radiation. The mutation work [S12] involved examining 13,052 children of proximally exposed parents and 10,609 children of control parents for rare electrophoretic variants of 30 blood proteins; three mutations were detected in each group in 725,587 and 539,170 equivalent locus tests, respectively. The mutation rates can therefore be estimated as $0.4\ 10^{-5}$ per locus (exposed group) and $0.6\ 10^{-5}$ per locus (control group). In a subset of 4,983 children of exposed parents (= 55,689 equivalent locus tests) and 5,026 control children (= 59,269 equivalent locus tests) who were studied for deficiency variants of nine erythrocyte enzymes, one mutant was encountered in the first group (rate: $1.80\ 10^{-5}$ per locus) and none in the second.

78. In cytogenetic studies [A1], among 8,322 children born to exposed survivors, 19 (0.23%) had sex-chromosomal anomalies (3 XYY, 7 XXY, 5 XXX, 3 mosaics and 1 miscellaneous), and 23 (0.28%) had structural rearrangements (10 Robertsonian translocations, 7 balanced reciprocal translocations, 1 inversion, 2 unbalanced supernumeraries and 3 miscellaneous unbalanced aberrations). Of 7,976 control children, 24 (0.30%) had sex-chromosomal anomalies (5 XYY, 9 XXY, 4 XXX, 3 mosaics and 3 miscellaneous) and 27 (0.34%) had structural rearrangements (6 Robertsonian translocations, 13 reciprocal translocations, 6 inversions and 2 miscellaneous unbalanced aberrations). Of the 11 balanced structural rearrangements for which family studies were made, one reciprocal translocation in each group was a new mutant, the rest were familial.

III. RISK COEFFICIENTS FOR GENETIC EFFECTS

79. All the numerical estimates of genetic risks discussed thus far have been obtained on the basis of genetically significant doses, i.e., on the assumption that the doses are received by individuals before or during the reproductive period. It is obvious that in the case of population exposures, the genetically significant doses are markedly less than the total doses received over a lifetime: damage sustained by germ cells of individuals who are beyond the reproductive period or who are not procreating for any other reason, poses no genetic risks. If it is assumed that the mean age at reproduction is 30 years and the average life expectancy at birth is 70-75 years, the dose received by 30 years is about 40% of the total dose.

80. To derive risk coefficients for genetic risks to a population, therefore, one needs to multiply the genetic risk estimates discussed earlier by 0.40. The following calculations make use of the most recent risk estimates presented in Table 7: (a) risk coefficient on the basis of gonadal dose in the reproductive segment of the population (from Table 7); for quantifiable damage only, over all generations, per Gy: ~12,000 per 10^6 or 1.2% ; (b) risk coefficient to the population; for quantifiable damage only, over all generations, per Sv ($1.2 \times 0.4 = 0.5$): 0.5%; (c) risk coefficient for the first two generations under conditions otherwise similar to (a) above (from Table 7): 3,100 per 10^6 or 0.3%; (d) risk coefficient to the population for the first two generations, per Sv (0.3×0.4): 0.1%. It is useful to reiterate here that these risk coefficients are for conditions of continuous exposure at a finite rate every generation and that they also reflect the total genetic risk from a once-only exposure of the parents.

IV. ESTIMATES OF DETRIMENT

81. The estimates of risk discussed in the preceding sections refer to the expected number of cases of serious genetic disease due to radiation-induced muta-

tions and chromosomal aberrations in the progeny of irradiated parents. The Committee had always realized (although it had not explicitly stated so in Reports prior to 1982) that presenting numerical estimates is just one aspect of risk estimation. Without some objective and quantifiable indicators of severity, it is difficult to perceive the impact of these on the individual and on the society at large and to make comparisons with the risks of induction of other biological effects, such as cancer. Therefore, starting with the UNSCEAR 1982 Report, the Committee began a systematic review of data bearing on this problem, focusing on spontaneously arising Mendelian, chromosomal and other diseases in order to gain some perspective of the detriment associated with these diseases and hoping to be able to use this knowledge to assess the impact of radiation-induced diseases at some later stage.

82. Particularly important in this context are the rough estimates of the disability caused and the length of life lost by the more common genetically determined (i.e., Mendelian and chromosomal) diseases provided by Carter [C4] and discussed in the 1982 Report. Carter's analysis revealed that for monogenic diseases (autosomal dominants, X-linked recessives and autosomal recessives) and for an estimated total birth prevalence of 12,500 per 10^6, about 190,000 years of life are lost, 300,000 years of life are potentially impaired and about 150,000 years of life are actually impaired per 10^6 live births. For chromosomal diseases, Carter's figures are about 89,000 years (lost life), 180,000 years (potentially impaired life) and about 90,000 years (actually impaired life) per 10^6 live births. The average life expectancy at birth assumed in these calculations was 70 years.

83. Czeizel and Sankaranarayanan [C5] extended this analysis to spontaneously arising congenital anomalies in man (these results are discussed in the UNSCEAR 1986 Report [U7]). The data on birth prevalences for the various conditions considered were derived from several epidemiological surveys carried out in Hungary and from the Hungarian Congenital Malformation Registry. Most of the information on mortality profiles was obtained from the records of the Hungarian Central Statistical Office in Budapest. Their analysis showed that with an estimated prevalence of about 60,000 per 10^6 live births in Hungary, the congenital anomalies may cause about 480,000 years of lost life, about 3,700,000 years of potentially impaired life (including congenital dislocation of the hip, whose birth prevalence is 25,770 per 10^6; and which, if excluded, would reduce the potentially impaired life figure to about 1,800,000 years) and about 4,500 years of actually impaired life. In these calculations, it has been assumed that the average life expectancy at live birth is 70 years.

V. UNCERTAINTIES AND PERSPECTIVES

84. The foregoing discussion amply documents the fact that there have been only a few changes in the numerical estimates of risk since the UNSCEAR 1977 Report. However, this statement is not meant to imply that there have been no advances in our knowledge in the areas relevant to genetic risk evaluation in recent years; rather, it reflects the fact that the impact of these advances has still not been fully assessed, as illustrated below.

A. PREVALENCE OF MENDELIAN, CHROMOSOMAL AND OTHER DISEASES

1. Mendelian diseases

85. There is no need to belabour the point that a sound knowledge of the contribution of gene mutations and of chromosomal aberrations to genetic diseases is of paramount importance, not only because it affords a perspective on those diseases to which man is literally heir, but also because it provides a frame of reference within which to appraise the increases expected as a result of radiation (or other mutagenic exposures). Our current estimates of prevalences of Mendelian diseases are based on a total of about 50 entities, the individual birth frequencies of which range from about $1\ 10^{-5}$ to about $1\ 10^{-4}$, with some upward adjustment in the total frequency for those diseases yet to be discovered. For obvious reasons, these estimates pertain to a very small proportion of those listed in the recent update of the McKusick compendium [M4] (i.e., a total of 1,906 conditions that are well documented as being inherited in a Mendelian manner and a further 2,001 for which such evidence is incomplete). The disparity is even greater when one considers that the total amount of nuclear DNA in the human haploid genome is about $3\ 10^6$ kb, which in principle can accommodate between 100,000 and 150,000 genes (on the assumption that an "average" gene is 20-30 kb long). However, this estimate is probably too high, since it neglects introns, pseudogenes, highly repetitive sequences such as satellite DNA and other interspersed and non-transcribed DNA sequences [B7, D2, E5, E6, J1]. Judging from the phenomenal progress in the understanding of the human genome that has been made possible in recent years by applying the methods of recombinant DNA technology (reviewed in the UNSCEAR 1986 Report [U7]), one can confidently look forward to (a) a better understanding of the relationship between genes and mutations and their effects on health and disease and (b) the application of the knowledge so derived to the evaluation of genetic risk.

2. Chromosomal diseases

86. At the chromosomal level, the application of banding techniques to the study of human chromosomes has led to the identification of a variety of chromosomal defects, particularly deletions and duplications involving every chromosome of the human complement (reviewed in the UNSCEAR 1977 Report [U7]). However, since most of the currently available information on these anomalies is in the form of case reports, their prevalences and their contribution to disease states cannot be readily determined. Of particular interest are microdeletions observed in mal-

formed children, especially those predisposed to a number of cancers. They provide new ways to localize and characterize important genes involved in pathology, both at the chromosomal and molecular levels. They also suggest that a pathological character may result from the presence of a pre-existing abnormal allele and a somatic mutation.

87. One exciting development in human cytogenetics in recent years has been the discovery of fragile sites on chromosomes, which can be made visible by appropriate culturing techniques (reviewed in the UNSCEAR 1982 and 1986 Reports [U6, U7]). As was already mentioned, the fragile site on the X-chromosome (at position Xq27) has elicited considerable attention because it is associated with one form of X-linked mental retardation. The prevalence of fragile-X-associated mental retardation has been estimated to be about $4\ 10^{-4}$ both in males and females [S6]: this would make the fragile-X the second most common (after Down's syndrome) chromosomal abnormality associated with mental retardation. It is currently not known whether this abnormality can be induced by radiation, so no genetic risk assessments can be made.

3. Congenital anomalies and other diseases of complex aetiology

88. Previous estimates of the prevalence of diseases of complex aetiology (i.e., congenital anomalies (43,000 per 10^6) and other multifactorial diseases (47,000 per 10^6) are based on the results of the British Columbia survey [T1], in which the follow-up period was from birth to age 21. Recent studies of Czeizel and Sankaranarayanan ([C1] and Czeizel et al. [C7]; discussed in the UNSCEAR 1986 Report [U7]) lend credence to the view that the above prevalence figures (in particular those of the "other multifactorial diseases") are underestimates. Their data show that in Hungary (a) congenital anomalies have a prevalence of about 60,000 per 10^6 live births and (b) the "other multifactorial" diseases may have a prevalence of about 600,000 per 10^6 population when all individuals up to age 70 are included. It should be made clear that the latter figure refers to the number of diseases per 10^6 and not to affected individuals; thus, some individuals have more than one disease.

89. As was discussed in the UNSCEAR 1986 Report (Annex C, paragraphs 51-58; see also Kalter and Warkany [K2]), the congenital anomalies can be subdivided, on the basis of their aetiology, into those caused by: (a) major genes (6% of the total of 60,000 per 10^6); (b) multiple factors (50% of the total); (c) chromosomal anomalies (5% of the total); and (d) environmental, including maternal, factors (6% of the total). About 30% of the anomalies recorded at birth have no known cause at present. One should add, however, that even for those congenital anomalies whose transmission patterns are consistent with a multifactorial aetiology (i.e., those resulting from an interplay of polygenic genetic predisposition and environmental factors), little is known of the mechanisms by which genetic predisposition acts or of the environmental factors involved.

90. The same is true of the "other multifactorial diseases" whose population prevalence has been estimated to be about 600,000 per 10^6. The question of whether and to what extent the prevalence of all these multifactorial diseases will increase as a result of radiation exposures remains a matter of conjecture. Our ability to make reliable estimates for these diseases depends largely on establishing the role of genetic factors in their aetiology. While no quantum leaps are expected in this area, there are persuasive, if not yet compelling, reasons to believe that it may soon be possible to estimate the mutation component in some of the seemingly multifactorially inherited diseases. The use of restriction fragment analysis and the development of more rapid methods for sequencing DNA will, in time allow a search for mutational variation at specific loci known to be involved which contribute to the occurrence of these diseases. The following examples are illustrative.

91. In a large Icelandic family (over 200 members in four living generations) showing Mendelian inheritance of X-linked secondary cleft palate and ankyloglossia ("tongue-tied"), Moore et al. [M10] localized the gene to Xq13-Xq21; the eventual cloning of the cleft palate gene could become a starting point for the analysis of the genetic basis of this developmental abnormality. A similar analysis using restriction fragment length polymorphism in an Old Order Amish pedigree made it possible to localize a dominant gene conferring a strong predisposition to manic depressive illness (a form of affective psychosis) to the tip of the short arm of chromosome 11 [E9]; however, in three Icelandic kindreds [H3] and three North American pedigrees [D3] there was no linkage with any of the chromosome 11 probes used. The inference is that mutations at different loci are responsible for the manic depressive phenotype in the Amish and in the other two population groups studied. Two other areas with particular promise involve lipid metabolism, where it is already possible to specify the contribution of specific loci concerned with the apolipoproteins to the variation in cholesterol levels seen among individuals (see [B9] for a recent review) and the transport of sodium and potassium which looms large in the occurrence of essential hypertension (reviewed in [H4] and [W2]).

B. MUTATIONAL MECHANISMS AND DNA REPAIR

92. An increasingly important area of contemporary genetic research is that associated with the studies on movable genetic elements, the conceptual framework for which was laid by McClintock, over three decades ago, with her work on "controlling elements" in maize [M6, M9]. Now, movable genetic elements have been discovered in a number of prokaryotes and eukaryotes, and some of these elements have been characterized at the molecular level. The rapidly accumulating evidence shows that they play an important role in the genesis of spontaneous mutations and of chromosomal aber-

rations; this knowledge, in turn, is altering our concepts about mutational mechanisms and the stability of the genome (discussed in the UNSCEAR 1986 Report [U7]).

93. Information on mammalian interspersed repetitive DNA sequences and why they are (or have at one time been) considered to be mobile genetic elements has been the subject of a number of recent reviews [R8, S14, S15]. These putative mobile genetic elements are currently classified into two groups: SINEs (for *s*hort *in*terspersed *e*lement*s*), which are typically less than 500 base pairs long and LINEs (*l*ong *in*terspersed *e*lement*s*), which range in length from a few hundred base pairs up to 7,000. Examples of SINEs are the *Alu* in primates and the *B1* and *B2* in rodents; examples of LINEs are LINE-1 and THE-1 in primates. There is as yet no evidence that these sequences move from one genomic location to another or that they are associated with detectable phenotypic effects in mammals including the human species, but such evidence is good in bacteria, yeast and Drosophila.

94. Skowronski and Singer [S15] have argued that the dispersed positions of LINE-1 sequences between genes, in introns and in interrupting tandem arrays of species-specific satellites, as well as the target site duplications associated with many LINE-1 sequences, suggest that the sequences were mobile in the past (in an evolutionary sense); further, these authors have compiled a list of five instances of mammalian (dog, rat and mouse) polymorphic alleles that differ by the presence or absence of LINE-1 units. On the basis of all these data (and some unpublished data on the insertion of a LINE-1 unit into a *myc* allele in DNA from a human breast carcinoma), they suggest that the LINE-1 alleles are still capable of being inserted into genomic loci.

95. Concerning the effects of mutagens, including x rays, on the mobility of these transposable elements, the evidence at present is essentially negative, except in yeast: in this species, McClanahan and McEntee [M11] showed that DNA damage induced by UV-irradiation or 4-nitroquinoline-1-oxide stimulates transcription of specific genes that share homology with the *Ty1* (the yeast transposons) element, the inference being that one or more members of the *Ty1* element is (are) regulated transcriptionally by DNA damage. More recently, Morawetz [M12] showed that *Ty1* insertion mutations at the *ADH-2* locus could be increased by UV- or gamma-irradiation or by treatment with ethyl methanesulphonate in a dose-dependent manner, the latter being the strongest agent in this regard.

96. The relevance of the findings in experimental systems—that is, that mobile genetic elements significantly contribute to "spontaneous mutations" and that mutagens have negligible or no effect on the mobility of these elements—to genetic risk evaluation in man has been addressed by Sankaranarayanan [S10, S16]. He argues that (a) if a major proportion of spontaneous mutations in man that lead to disease states is due to the insertion of mobile genetic elements and if the mobility of these is unaltered by radiation exposures, then some of the principal assumptions of the doubling dose method for genetic risk evaluation would lose their validity; (b) currently, however, there is no evidence that documents a significant role for mobile genetic elements in the origin of spontaneous mutations in man; and (c) consequently, there is no need to abandon the use of the doubling dose method for risk evaluation on these grounds.

97. In the realm of DNA repair, one of the principal questions being addressed by current research is the influence of function or activity of a DNA sequence and its repair following mutagen treatment. All these studies have so far been carried out primarily with mammalian cell lines and UV-irradiation. The findings of interest are (a) there is preferential repair of active (transcribing) genes relative to the genome as a whole [B8]; (b) the regions of active repair, in the system studied, correspond to control regions and the 5′ ends of the transcription unit; and (c) in regions away from the 5′ or 3′ ends of the genes, repair is less efficient [S17 and the papers cited therein]. Indirect evidence for preferential repair of active genes has also been presented by Mullenders et al. [M13, M14]. These and other results support the view that ". . . damage in silent regions of the genome may have greater potential for engendering mutations and DNA rearrangements than damage in or near transcription units" [S17]. The generality of these findings and their implications for germ cell mutagenesis with ionizing radiation remain to be established.

C. NATURE OF SPONTANEOUS AND RADIATION-INDUCED MUTATIONS

98. The methods of recombinant DNA technology have enabled the direct detection of the molecular heterogeneity of spontaneously arising mutational events that lead to disease states in man, as will be evident from the spectacular progress in studies of the globin genes (see, for example, [O3]). Similar studies are being carried out to analyse the nature of radiation-induced mutations in mammalian somatic cells (e.g., [V1, T2]). Most of these data have been discussed in the 1986 Report [U7]. An important technical advance has recently been made that allows the cloning and sequencing of small specific DNA segments from total genomic DNA after in vitro amplification of those segments up to 200,000-fold (the so-called polymerase chain reaction, or PCR [S18]). The use of this technique in induced mutagenesis studies will allow mutation spectra to be determined with great precision [V2].

D. FRAGILE SITES AND SPONTANEOUS CHROMOSOME BREAKAGE

99. There are suggestive indications for the thesis that certain autosomal fragile sites may predispose to chromosome breakage. Hecht and Hecht [H1, H2] have adduced some evidence in this regard by analysing information on the location of breakpoints leading to chromosomal anomalies (deletions, duplications, inversions and non-Robertsonian translocations) found in amniocentesis studies and in studies on spontaneous

abortions, still births and new-borns. They caution, however, that in view of the heterogeneity of the data-base from which the pertinent information was extracted, more evidence is needed to determine whether fragile sites are regions in the chromosome predisposed to breakage in the germ cell lineage. The question of whether those fragile sites may predispose the chromosomes to radiation-induced breakage events is as yet unanswered.

E. ONCOGENES: GENETIC ASPECTS

100. The remarkable insights into oncogenic transformation that have emerged in recent years (reviewed in the UNSCEAR 1986 Report [U7]) amply testify to the fact that cancer studies have become an exciting area for both geneticists and cancer biologists. There is now extensive evidence that mammalian genomes harbour nucleotide sequences related to the retroviral oncogenes as part of their normal genetic make-up, that several of them play an active role in the regulation and control of cellular proliferation and that their activation (either spontaneously or through mutagenic exposures) can initiate cancer. There is thus no a priori reason to assume that germ cells will be immune in this respect, especially after exposure to mutagens. Nomura [N3, N5] has reported high tumour yields in the progeny of irradiated mice and thus has highlighted the possibility that genetic changes induced in the germ cells of parents can cause tumours in progeny. It would therefore appear important to confirm these studies independently in experimental systems. Whether this component of genetic risks would be negligible, small or significant for man is difficult to say at present.

F. OTHER WORK IN PROGRESS

101. Data on chromosomal abnormalities studied through direct analyses of the chromosome complement of human spermatozoa (from normal men as well as from those undergoing radiotherapy) after in vitro fertilization of hamster eggs were discussed in the UNSCEAR 1982 and 1986 Reports [U6, U7]. This technique has now been considerably improved [K3] and extended to studies using human spermatozoa irradiated in vitro [K4, M15]. In these studies, which used spermatozoa from five healthy donors, the frequencies of spermatozoa with structural chromosomal aberrations were found to increase linearly with the x-ray dose (0 Gy, 14.1%; 0.25 Gy, 18.9%; 0.5 Gy, 28.5%; 1 Gy, 42.6% and 2 Gy, 68.0%; total numbers of karyotyped spermatozoa: 0 Gy, 2,097; 0.25 Gy, 491; 0.5 Gy, 543; 1 Gy, 819; 2 Gy, 1,009). Most of the x-ray-induced aberrations were breaks and fragments, but a few translocations (0.03-0.1 per cell) were also found; there was no decrease in the fertilization rate of irradiated spermatozoa, even at the highest dose, 2 Gy. Clearly, this kind of study has relevance to the assessment of genetic risks associated with the induction of chromosomal aberrations.

102. Genetic studies on the Hiroshima and Nagasaki populations are continuing and will remain a major source of direct human data. An international collaborative programme on genetic effects in the offspring of cancer patients exposed to physical and chemical agents for therapeutic purposes is being initiated [L2, O2]. This is a commendable enterprise: it is hoped that it will provide information on hazards attributable to genetic damage in human germ cells, and it will undoubtedly have practical importance for clinicians who must advise cancer survivors or current cancer patients who are pregnant or considering pregnancy. Likewise, the follow-up of persons exposed to radiation in the Chernobyl nuclear power plant accident (and their progeny) that is currently underway in the U.S.S.R. is a worthwhile undertaking.

103. The work of Dobson and colleagues over the past several years has suggested that the exceptionally high sensitivity of mouse immature oocytes to killing by radiation is a consequence of the possibility that the target for killing is not the nucleus but the plasma membrane. More recent results by the same group support this idea [S19, S20]. Furthermore, Dobson et al. [D4] have now reported, using monoenergetic 0.43 MeV neutrons and ^{252}Cf (whose recoil protons have subcellular track lengths of such a nature that the radiation energy can be deposited in the DNA in a calculable fraction of the oocytes that survive), that chromosomal aberrations can be recovered from irradiated immature oocytes and that these are similar to those from mature oocytes. A similar effect has also been reported by Griffin et al. [G2].

G. SUGGESTIONS FOR FUTURE RESEARCH

104. In this Annex, the progress that has been made in areas pertinent to the evaluation of genetic radiation hazards in man has been reviewed and estimates of genetic risks have been presented. The Committee feels that, in order to increase precision in risk assessment, more research effort along the following lines will be useful (the order in which these are listed does not reflect the order of importance): (a) molecular analysis of spontaneous and induced mutations in somatic and germ cells with and without repair; (b) further studies relevant to the genetic radiosensitivity of human oocytes; (c) phenotypic expression and transmission of induced deletions and other relevant genetic changes; (d) a search for mammalian models to study human diseases with complex aetiology; (e) tests on the validity of the assumptions and correction factors used in genetic risk estimation; (f) further in-depth analysis of multifactorial diseases with respect to the mutation component; (g) mechanisms underlying non-disjunction and chromosome loss and effects of radiation on these genetic changes; (h) further work bearing on total genetic damage manifesting in the first generation after radiation exposure; (i) relationships between radiation dose, dose-rate and quality and types of induced chromosomal aberrations; (j) development of methods to reveal chromosomal aberrations and gene mutations in human germ cells in the haploid stage; and (k) the use of transgenic mice to study DNA repair deficiencies and mutational mechanisms.

Table 1

Summary of genetic risks estimated
in the BEIR 1972 Report using the doubling dose method

The effects are those estimated for a population continuously exposed
at a rate of 1 rem per generation (low-LET, low dose rate)
in a population of 1 million live births.

Assumed doubling dose range: 20-200 rem

Disease classification	Current incidence per 10^6 live births	Effect of 1 rem per generation	
		First generation	Equilibrium
Dominant diseases	10000	10-100	50- 500
Chromosomal and recessive diseases	10000	Relatively slight	Very slow increase
Congenital anomalies	15000		
Anomalies expressed later	10000	1-100	10-1000
Constitutional and degenerative diseases	15000		
Total	60000	10-200	60-1500

Table 2

Summary of genetic risks estimated
in the UNSCEAR 1977 Report using the doubling dose method

The effects are those estimated for a population continuously exposed
at a rate of 1 rad per generation (low-LET, low dose rate)
in a population of 1 million live births.

Assumed doubling dose: 100 rad

Disease classification a/	Current incidence per 10^6 live births b/	Effect of 1 rad per generation	
		First generation c/	Equilibrium
Autosomal and X-linked diseases	10000	20	100
Recessive diseases	1100	Relatively slight	Very slow increase
Chromosomal diseases	4000 d/	38 e/	40
Congenital anomalies			
Anomalies expressed later	90000 f/	5 g/	45 g/
Constitutional and degenerative diseases			
Total	105100	63	185
Percentage of current incidence		0.06	0.17

a/ Follows that given in the BEIR Report [B1].
b/ Based on the results of the British Columbia Survey with certain modifications.
c/ The first generation increase is assumed to be about one fifth of the equilibrium incidence for autosomal dominant and X-linked diseases; for those included under the heading "congenital anomalies etc." it is one tenth of the equilibrium incidence.
d/ Based on the pooled values estimated from cytogenetic surveys of new-born children; includes mosaics but excludes balanced translocations.
e/ The first generation increase is assumed to include all the numerical anomalies and three fifths of the unbalanced translocations (the remaining two-fifths being derived from a balanced translocation in one parent).
f/ Includes an unknown proportion of numerical (other than Down's syndrome) and structural chromosomal anomalies.
g/ Based on the assumption of a 5% mutational component.

Table 3

Genetic effects of an average population exposure of 1 rem per 30-year generation estimated in the BEIR 1980 Report using the doubling dose method

Assumed doubling dose range: 50-250 rem

Type of genetic disease a/	Current incidence per 10^6 live births	Effect of 1 rem per generation per million live-born offspring	
		First generation b/	Equilibrium c/
Autosomal dominant, X-linked	10000	5-65 d/	40-200
Irregularly inherited	90000		20-900 e/
Recessive	1100	Very few; effects in heterozygotes accounted for in top row	Very slow increase
Chromosomal aberrations f/	6000	Fewer than 10 g/	Increases only slightly

a/ Includes disorders and traits that cause serious handicap at some time during lifetime.
b/ Estimated directly from measured phenotypic damage or from observed cytogenetic effects.
c/ Estimated by the relative mutation risk method.
d/ No first-generation estimate available for X-linked disorders; the expectation is that it would be relatively small.
N.B.: A typographical error in the BEIR Report is corrected here.
e/ Some estimates have been rounded off to dispel an impression of considerable precision.
f/ Includes only aberrations expressed as congenital malformations, resulting from unbalanced segregation products of translocations and from numerical aberration.
g/ Majority of the Sub-Committee feels that it is considerably closer to zero, but one member feels that it could be as much as 20.

Table 4

Cases of serious genetic ill health in offspring (excluding abortions) from parents irradiated with 1 million man-rem in a population of constant size, estimated by the 1980 ICRP Task Group

Category of genetic effect	Equilibrium a/	First generation plus second generation
Unbalanced translocations; risk of malformed live born	30	23 + 6 = 29
Trisomics and XO	30	30 + 0 = 30
Simple dominants and sex-linked mutations	100	20 + 16 = 36
Dominants of incomplete penetrance and multifactorial disease maintained by mutation	160 b/	16 + 14 = 30
Multifactorial disease not maintained by mutation	0	0
Recessive disease	c/	c/
Total	320	89 + 36 = 125

a/ Over all generations following the generation exposed.
b/ The sum of the three entries above (i.e., 30 + 30 + 100).
c/ No estimates given.

Table 5

Effects of 10^{-2} Gy per generation of low-LET, low-dose-rate irradiation in a population of 1 million live-born estimated in the UNSCEAR 1982 Report using the doubling dose method

Assumed doubling dose: 1 Gy

Disease classification a/	Current incidence per million b/	Effect of 10^{-2} Gy per generation	
		First generation c/	Equilibrium
Autosomal dominant and X-linked diseases	10000 d/	15	100
Autosomal recessive diseases	2500 e/	Slight	Slow increase
Chromosomal diseases			
Structural	400 f/	2.4	4
Numerical	3000 g/	Probably very small	Probably very small
Congenital anomalies, anomalies expressed later and constitutional and degenerative diseases	90000 h/	4.5	45 i/
Total	105900	~ 22	~ 150

a/ Follows that given in the 1972 BEIR Report [B1], except that chromosomal diseases are divided into those with a structural and those with a numerical basis.
b/ Based on the results of the British Columbia survey and other studies.
c/ The first generation increment is assumed to be about 15% of the equilibrium incidence for autosomal dominant and X-linked diseases, about three fifths of the equilibrium incidence for structural anomalies and about 10% of the equilibrium incidence for diseases of complex inheritance.
d/ Includes diseases with both early and late onset.
e/ Also includes diseases maintained by heterozygous advantage.
f/ Based on the pooled values from cytogenetic surveys of new-borns but excluding euploid structural rearrangements, Robertsonian translocations and "others" (mainly mosaics).
g/ Excluding mosaics.
h/ Includes an unknown proportion of numerical (other than Down's syndrome) and structural chromosomal anomalies.
i/ Based on the assumption of a 5% mutational component.

Table 6

Genetic risks of low-dose, low-dose-rate, low-LET irradiation estimated in the NUREG 1985 Report

Assumes a 0.01 Gy dose to the population.
Note that the first-generation increases were estimated directly from measured phenotypic damage; the entries given in column "all generations" were derived using the doubling dose method assuming a doubling dose of 1 Gy.

Type of disorder	Normal incidence a/	Risk of 0.01 Gy b/	
		First generation c/	All generations
Single gene	4800		
Autosomal dominant		15 d/	70
X-linked		5	30
Irregularly inherited	43200	d/	70 e/
Chromosome aberrations f/	2880		
Aneuploidy		4	5
Unbalanced translocations		6	10
Total (rounded)	50900	30	185

a/ For a total population of 10^6 persons (16,000 live births/year) for 30 years (480,000 live births).

b/ Cases expected in each generation of children from a population of 10^6 persons, each receiving a dose of 0.01 Gy; assumes 30-year intergenerational interval and birth rate of 16,000 per year per 10^6 persons, or 480,000 children per generation; the integrated risk over all generations following a parental dose of 0.01 Gy is the same as the risk at equilibrium (the column marked "all generations") when the population is exposed at a rate of 0.01 Gy per generation.

c/ Estimated directly from measured phenotypic damage.

d/ First generation increase in irregularly inherited disorders included within that for autosomal dominant disorders.

e/ Based on a doubling dose of 1 Gy and 10 generations mean persistence time, which is very uncertain.

f/ Includes only aberrations expressed as congenital malformations resulting from unbalanced translocations (2,400/480,000) and from aneuploidy (480/480,000); equilibrium time of 1-2 generations and 1 generation, respectively.

Table 7

Risks of genetic disease per 1 million live-births in a population exposed to a genetically significant dose of 0.01 Gy per generation of low-dose-rate, low-dose, low-LET irradiation estimated in the UNSCEAR 1986 Report using to the doubling dose method

Assumed doubling dose: 1 Gy

Disease classification	Current incidence per 10^6 livebirths a/	Effect of 0.01 Gy per generation		
		First generation b/	Second generation c/	All generations (equilibrium) d/
Autosomal dominant and X-linked diseases	10000	15	13	100
Autosomal recessive diseases	2500			
- Homozygous effects		No increase	No increase	11 e/
- Partnership effects		Negligible	Negligible	4 f/
Chromosomal diseases due to structural anomalies	400	2.4	1	4
Subtotal (rounded)	13000	18	14	115
Early acting dominants g/	Unknown	]		
Congenital anomalies h/	60000	]		
Other multifactorial diseases i/	600000	]	Not estimated	
Heritable tumours j/	Unknown	]		
Chromosomal diseases due to numerical anomalies k/	3400	]		

a/ Based on the results of the British Columbia Study and other studies; for details see [U5].

b/ The first-generation increment is assumed to be 15% of that at equilibrium for autosomal dominant and X-linked diseases and three fifths of that at equilibrium for chromosomal diseases due to structural anomalies.

c/ Not given in the UNSCEAR 1986 Report and estimated here; for autosomal dominants and X-linked diseases, it is calculated as 15% of (equilibrium increase minus the increase in the first generation); a similar procedure applies to chromosomal diseases due to structural anomalies.

d/ These values apply if 0.01 Gy is given in each generation, but they also express the total genetic damage over all generations if the dose of 0.01 Gy is given in one generation.

e/ Frequency of recessives maintained by mutation assumed to be 1100 per 10^6 livebirths.

f/ From partnership between induced mutations and those already present in the population, assuming 2.5% heterozygous disadvantage and a mean number of harmful recessives per gamete of 1 [S9].

g/ The incidence of these in human populations is unknown because they act too early to be recognized as transmissible dominants; they include dominant sub-lethals, the rate for which has been estimated to be 5-10 per 0.01 Gy of paternal irradiation of mice (see Table 23 of the UNSCEAR 1986 Report [U7]).

h/ Studies by Lyon and Nomura and colleagues show that, in the mouse, they are induced by irradiation of male and female germ cells, but the associated risks appear to be low.

i/ The prevalence is much higher than that given in previous UNSCEAR Reports, because diseases manifest up to age 70, instead of mainly to age 21, have now been included, together with some less serious conditions. Furthermore, the figure denotes the number of diseases per 10^6 individuals and not the number of affected individuals. There is considerable uncertainty over whether a doubling dose of 1 Gy and a mutational component of 5% (as used previously) can be justified. The UNSCEAR 1982 Report arrived at estimates of 4.5 extra cases per 1 million in the first generation and 45 per million at equilibrium after a parental dose of 0.01 Gy, on the basis of the previous estimate of population prevalence of 90,000 per million.

j/ Nomura has reported the induction of pulmonary and other tumours in the F_1 generation of mice after irradiation (see [U7] for details), but these have very low expressivity; their likely effects on health are thus unclear.

k/ It is still not clear whether germinal irradiation leads to significantly increased frequencies of non-disjunction, but any resultant genetic risk from the production of trisomic conditions is thought to be low.

Table 8

Summary of genetic risks estimated
in the UNSCEAR 1972 Report using the direct method

The estimates are per rad of low-LET, low-dose-rate radiation exposure.

End point	Expected rate of induction per million		Expression in F_1 per million conceptions after spermatogonial irradiation
	Spermatogonia	Oocytes	
Recessive point mutations	1500 a/	Very low	30-75
	(36) b/	-	(1-2)
Dominant visibles	2	-	2
Skeletal mutations	4	-	c/
Reciprocal translocations d/	15 e/	Very low	2 congenitally malformed children, 19 unrecognized early embryonic losses, 9 recognized abortions f/
X-chromosome losses	Very low	8	8 early embryonic and/or abortions
Other chromosome anomalies	Very low	-	Very low
Total genetic damage	1521 g/		
	(57) h/		
Total genetic damage' i/	300 i/		6-15 i/

Note: Dashes indicate that inadequate or no information is available.

a/ Estimate based on mouse specific locus data.

b/ Estimate based on the per genome rate for recessive lethals induced in mouse spermatogonia.

c/ Included under recessive point mutations.

d/ Figures apply to low-dose x-irradiation. Estimates for chronic gamma-irradiation are 50% lower.

e/ Balanced products.

f/ For low-dose x-irradiation; for chronic gamma-irradiation, figures should be halved.

g/ Obtained by adding 1500+2+4+15 in the column.

h/ Obtained by adding 36+2+4+15 in the column.

i/ Relative to spontaneous incidence of genetic diseases among live born, based on an estimated "doubling dose" of 100 rad.

j/ In terms of incidence of genetic disease among live born (doubling dose method).

Table 9

Summary of genetic risks estimated in the UNSCEAR 1977 Report using the direct method

The estimates are per rad of low-LET, low-dose-rate radiation exposure.

End point	Expected rate of induction per million		Expression in F_1 per million conceptions after spermatogonial irradiation
	Spermatogonia	Oocytes	
1. Autosomal mutations a/	60	-	20 d/
2. Dominant visibles b/	Very low	-	
3. Skeletal mutations c/	4	-	
4. Balanced reciprocal translocations e/	17- 87	Low	Low f/
5. Unbalanced products of end-point 4 above	34-174	-	2-10 g/
6. X-chromosome loss h/	Very low	Low	Low
7. Other chromosome anomalies	-	-	-

Note: Dashes indicate that inadequate or no information is available.

a/ Presumed to include small deficiencies. Based on rate of induction of mutations in mice that are lethal in the homozygous condition, which is doubled to give the overall rate.

b/ Based on those scored in the course of specific-locus experiments in mice.

c/ Detected in mice by dominant effects.

d/ Overall rate of dominant effects, based on skeletal mutations and presumably including dominant visibles and heterozygous effects of autosomal mutations.

e/ Derived from human and marmoset cytogenetic data under the assumption that the frequency of translocations in the F_1 progeny is one fourth of that observed in spermatocytes.

f/ Effects such as those given for end-point 5 in the next footnote will become manifest in generations following the first.

g/ Expressed as congenital malformations. In addition, there would be 11-55 recognized abortions and 22-109 early embryonic losses.

h/ Detected in mice by X-chromosomal markers.

Table 10

Summary of genetic risks estimated
in the UNSCEAR 1982 Report using the direct method

The estimates are per 10^{-2} Gy of low-LET, low-dose-rate radiation exposure.

Risk associated with	Expected frequency (per 10^6) of genetically abnormal children in the first generation after irradiation of	
	Males	Females
Induced mutations having dominant effects a/	~10 to ~20 b/	0 to ~9 c/
Unbalanced products of induced reciprocal translocations	~0.3 to ~10 d/	0 to ~3 e/

a/ Includes the risk from the induction of dominant mutations, as well as of recessive mutations, deletions and balanced translocations with dominant effects.

b/ The lower limit of ~10 is derived from data on cataract mutations and the upper limit of ~20 per 10^6 is derived from data on skeletal mutations and is the same as the one arrived at in the 1977 report. A multiplication factor of 2 has been used in the skeletal estimate but not in the cataract one; this factor is an attempt to allow for the likelihood that many dominant mutations (especially those affecting systems other than the skeleton) remain to be detected. A correction factor of 0.5 to allow for skeletal mutations which are not clinically significant is not required for the cataract estimate.

c/ The lower limit of zero is based on the assumption that the mutational sensitivity of human immature oocytes is similar to that of mouse immature oocytes; the upper limit of 9 per 10^6 is based on the assumption that the sensitivity of the human oocytes is similar to that of the mature and maturing oocytes and that the latter is 0.44 times that of spermatogonia. See text for further details.

d/ The lower limit of ~0.3 per 10^6 is based on rhesus monkey cytogenetic data; the upper limit of ~10 per 10^6 is based on combined marmoset and human cytogenetic data.

e/ The lower limit of zero is based on the assumption that the sensitivity of the human immature oocytes to the induction of heritable reciprocal translocations will be similar to that of the mouse immature oocytes with respect to the induction of chromosome aberration phenomena; the upper limit of ~3 per 10^6 is based on the assumptions that the sensitivity of the human immature oocytes to the induction of translocations will be one half that of the human and marmoset spermatogonia (based on results with mice on heritable translocations), that the frequency of unbalanced products will be six times that of recoverable balanced reciprocal translocations and that 6% of the unbalanced products will result in congenitally malformed children.

Table II

Risks of induction of genetic damage in man per 10^{-2} Gy
at low dose rates of low-LET radiation
estimated in the UNSCEAR 1986 Report using the direct method

Risk associated with	Expected frequency (per 10^6) of genetically abnormal children in the first generation after irradiation of	
	Males	Females
Induced mutations having dominant effects a/ b/	~ 10 to ~ 20 c/	0 to ~9 d/
Induced recessive mutations e/	0	0
Unbalanced products of induced reciprocal translocations	~ 1 to ~ 15 f/	0 to 5 g/

Note: These estimates are the same as those made in the UNSCEAR 1982 Report except for changes indicated in footnotes b/ and e/.

a/ Includes risk from the induction of dominant mutations, as well as of deletions and balanced reciprocal translocations with dominant effects.

b/ Does not include the risk of mortality (between birth and early life) estimated on the basis of data on litter size reduction in mice (about 5-10 cases per million conceptions); see text for details.

c/ The lower limit is derived from the data on cataract mutations and the upper limit from those on skeletal mutations (both in mice); the latter is the same as that arrived at in the UNSCEAR 1977 report [U5]. A multiplication factor of 2 has been used in the skeletal estimate, but not in the cataract one. This factor is an attempt to allow for the likelihood that many dominant mutations (especially those affecting bodily systems other than the skeleton) remain to be detected. A correction factor of 0.5, which allows for skeletal mutations that are not clinically significant, is not required for the cataract estimate. See UNSCEAR 1982 Report [U6] for details.

d/ The lower limit of zero is based on the assumption that the mutational sensitivity of human immature oocytes is similar to that of mouse immature oocytes; the upper limit of ~9 is based on the assumption that the sensitivity of the human oocytes is similar to that of mature and maturing mouse oocytes and that the latter is 0.44 times that of spermatogonia. See UNSCEAR 1982 Report for details.

e/ Although the risk (of recessive disease from the induction of recessive mutations) is zero in the first generation, about 1 extra case per million live births would be expected in the following 10 generations (from partnership effects) and on certain assumptions, about 10 extra cases per 1 million would be expected by the tenth generation (from effects due to identity by descent). See text for further details.

f/ The lower limit is based on combined cytogenetic data from chronic low-LET irradiation experiments involving the rhesus monkey and the crab-eating monkey, and the upper limit, on the combined human and marmoset (Saguinus fuscicollis) cytogenetic data (see UNSCEAR 1986 Report for details). It has been assumed that 9% of unbalanced products of reciprocal translocations will result in birth of congenitally abnormal children.

g/ The lower limit of zero is based on the assumption that the sensitivity of the human immature oocyte to the induction of heritable reciprocal translocations will be similar to that of mouse immature oocytes with respect to the induction of chromosome aberration phenomena; the upper limit is based on the assumptions that (a) the sensitivity of the human immature oocytes to the induction of reciprocal translocations will be one half that of the human and marmoset spermatogonia (based on results with mice on heritable translocations); (b) the frequency of unbalanced products will be six times that of recoverable balanced reciprocal translocations; and (c) about 9% of unbalanced products will result in congenitally malformed children. See UNSCEAR 1982 Report for details.

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